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Opinion of the Scientific Committee on Food on chemically defined flavouring substances listed in the EU register

Flavouring Group Evaluation 2 (FGE.02):
Branched- and straight-chain aliphatic saturated primary alcohols, aldehydes and related esters of primary alcohols and straight-chain carboxylic acids from chemical groups 1 and 2 (Commission Regulation (EC) No 1565/2000 of 18 July 2000)

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FLAVOURING GROUP EVALUATION 2

BRANCHED- AND STRAIGHT-CHAIN ALIPHATIC SATURATED PRIMARY ALCOHOLS, ALDEHYDES AND RELATED ESTERS OF PRIMARY ALCOHOLS AND STRAIGHT-CHAIN CARBOXYLIC ACIDS FROM CHEMICAL GROUPS 1 AND 2

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Flavouring Group Evaluation 2

1. Introduction

1.1. Legal background

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a procedure for the establishment of a list of flavouring substances the use of which will be authorised to the exclusion of all others in the EU. In application of that Regulation, a register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2002/113/EC (EC, 2002a). The latter Decision introduced a new numbering system by attributing each flavouring substance an FL-number. Furthermore, all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000) which is based on the opinion of the Scientific Committee on Food (SCF, 1999). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

After the completion of the evaluation programme the positive list of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation No 2232/96).

1.2. Description

The present Flavouring Group Evaluation (FGE.02), using the procedure as referred to in the Commission Regulation (EC) 1565/2000 (the Procedure – shown in schematic form in Annex I), deals with 41 saturated alcohols, aldehydes and esters derived from aliphatic acyclic primary alcohols and linear aliphatic acyclic carboxylic acids. These 41 flavouring substances belong to chemical groups 1 and 2 of Annex I of Regulation (EC) No 1565/2000 (EC, 2000).

The 41 flavouring substances (candidate substances) are closely related structurally to 64 flavouring substances (supporting substances) evaluated at the 49th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in the group "Esters of Aliphatic Acyclic Primary Alcohols and Linear Aliphatic Acyclic Carboxylic Acids" (JECFA, 1998; JECFA, 1999b).

The flavouring substances under consideration in the present evaluation are listed in Tables 1 and 2, as well as their chemical names, FL-, CAS-, CoE-, FEMA-numbers, and structures. Five of the 41 flavouring substances are aliphatic acyclic primary alcohols [FL-no: 02.126, 02.154, 02.180, 02.196, and 02.202]; one is an aliphatic acyclic aldehyde [FL-no: 05.152] and 35 are esters of aliphatic acyclic primary alcohols and linear aliphatic acyclic carboxylic acids [FL-no: 09.307, 09.327, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.587 - 09.589, 09.592 - 09.594, 09.598, 09.600, 09.602, 09.642, 09.651, 09.659 - 09.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, and 09.820].

The names and structures for the 64 supporting substances are listed in Table 3, together with their evaluation status (CoE, 1992; JECFA, 1999b; SCF, 1995).

1.3. Stereoisomers

Nine of the 41 flavouring substances in the group possess a chiral centre [FL-no: 09.307, 09.358, 09.659, 09.660 - 09.662, and 09.664 - 09.666]. In each of these cases the substance has been presented without any indication that the commercial flavouring substance has dominance of one or the other isomer.

1.4. Natural food occurrence

Thirty-eight of the substances in the present group of 41 substances have been reported to occur in a wide variety of fruits, wines and liquors, as well as in cheese, juice and other foods (TNO, 2000). Quantitative data have been reported for 29 of these substances in foods comprising:

- up to 7 mg/kg tetradecanol [FL-no: 02.126] in whisky
- up to 5 mg/kg butyl decanoate [FL-no: 09.327] in oranges
- up to 0.14 mg/kg 2-methylbutyl dodecanoate [FL-no: 09.307] in cheese
- up to 0.05 mg/kg heptadecanol [FL-no: 02.154] in butter
- 0.003 mg/kg hexadecanal [FL-no: 05.152] in milk
- 0.009 mg/kg methyl octadecanoate [FL-no: 09.651] in milk powder

Three of the substances, isobutyl octadecanoate, pentyl dodecanoate and pentyl hexadecanoate [FL-no: 09.592, 09.681, and 09.682], respectively, have not been reported in foods by TNO (TNO, 2000).

2. Specifications

Purity criteria for the 41 candidate substances have been provided by the flavour industry (EFFA, 2001a) (see Table 1).

Judged against the requirements in Annex II of Commission Regulation EC no 1565/2000 (EC, 2000), this information is adequate for 30 of the 41 substances. The purity criteria for the remaining 11 substances are deficient in one or more parameters (see Table 1).

3. Estimated Daily per Capita Intake

The total annual volume of production of the 41 candidate substances from use as flavouring substances in Europe is approximately 338 kg (EFFA, 2001d) and for the 64 supporting substances 65,000 kg (cited in (JECFA, 1999b)).

On the basis of the annual volumes of production reported for the 41 candidate substances, the daily per capita intakes for each of these flavourings have been estimated (Table 2). More than 50 % of the total annual volume of production for the candidate substances (EFFA, 2001d) is accounted for by six of these flavourings: butyl decanoate [FL-no: 09.327], isobutyl decanoate [FL-no: 09.587], isobutyl octanoate [FL-no: 09.593], isopentyl decanoate [FL-no: 09.598], 2-methylbutyl propionate [FL-no: 09.665], and propyl octanoate [FL-no: 09.816]. The estimated daily per capita intake of butyl decanoate from use as a flavouring substance is approximately 8 microgram/day, that of isobutyl decanoate is approximately 4 microgram/day, that of isobutyl octanoate 4 microgram/day, that of isopentyl decanoate 5 microgram/day, that of 2-methylbutyl propionate 3 microgram/day, and that of propyl octanoate 3 microgram/day (Table 2).

According to the flavour industry (EFFA, 2001a) all of the candidate substances are used in flavoured food products in the following food categories (see Annex III in the Commission Regulation 1565/2000).

Food category	**Description**
Category 1.	Dairy products
Category 2.	Fats and Oils
Category 3.	Edible ices
Category 4.1.	Fruits*
Category 5.	Confectionery
Category 6.	Cereals and cereal products (except FL-no: 06.033, 06.049, 06.066)
Category 7.	Bakery wares
Category 8.	Meat and meat products
Category 9.	Fish and fish products (except FL-no: 06.127, 09.642)
Category 11	Sweeteners, including honey (only FL.-no: 06.096)
Category 12.	Salts, spices, soups, sauces, salads, protein products etc. (except FL-no: 06.096, 09.381)
Category 13.	Foodstuffs intended for particular nutricular uses
Category 15.	Ready-to-eat savouries (except FL-no: 06.177)
Category 16.	Composite foods, foods that could not be placed in categories 1 to 15 (except FL-no: 06.070)

*Subgroup of food category 4. “Processed fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes), and nuts and seeds”.

The normal use levels for the candidate substances are in the range of 1 – 50 mg/kg food, with maximum use levels of up to 350 mg/kg food in ready-to-eat savouries (EFFA, 2001a).

4. Absorption, Distribution, Metabolism and Elimination

Data for short and medium length linear- and branched-chain alcohols, aldehydes and esters (and their alcohol and carboxylic acid moieties), included in the present Flavouring Group Evaluation and general information for this class of chemicals indicate that they are rapidly absorbed from the gastrointestinal tract, metabolised and excreted. Also, in vitro hydrolysis data from studies with the supporting substances, as well as other closely related substances, indicate that the esters included in the present evaluation can be hydrolysed to yield the corresponding alcohols and carboxylic acids (Gangolli & Shilling, 1968; Grundschober, 1977; Leegwater & Straten, 1974; Longland et al., 1977).

General discussions on the biotransformation of linear aliphatic acids and aliphatic linear- and branched-chain alcohols and aldehydes, as well as hydrolysis of their esters, are provided in Annex II.

In summary, it is anticipated that the 35 candidate esters [FL-no: 09.307, 09.327, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.587 - 09.589, 09.592 - 09.594, 09.598, 09.600, 09.602, 09.642, 09.651, 09.659 - 9.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, and 09.820] will undergo hydrolysis to yield their corresponding aliphatic alcohols and linear carboxylic acids. The resulting aliphatic alcohols and linear carboxylic acids, as well as the five aliphatic alcohols [FL-no: 02.126, 02.154, 02.180, 02.196, and 02.202] and one linear aliphatic

aldehyde [FL-no: 05.152] are expected to be completely oxidised to carbon dioxide via the fatty acid pathway followed by the tricarboxylic acid cycle. The branched-chain alcohols can also be conjugated in part and excreted via the urine (Annex II).

5. Application of the Procedure for the Safety Evaluation of Flavouring Substances

The safety evaluation of the 41 candidate substances was conducted stepwise according to the Procedure and the results are summarised in Table 2.

Step 1.

All the 41 candidate substances from chemical groups 1 and 2 are classified in structural class I (Cramer et al., 1978), suggesting a low order of oral toxicity.

Step 2.

Step 2 requires consideration of whether detoxification pathways are available to safely metabolise the substances, at the expected levels of intake, to innocuous products. It is anticipated that the 35 esters [FL-no: 09.307, 09.327, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.587 - 9.589, 09.592 - 09.594, 09.598, 09.600, 09.602, 09.642, 09.651, 09.659 - 09.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, and 09.820], will be readily hydrolysed to their component alcohols and carboxylic acids. The resulting linear and branched chain aliphatic alcohols and linear carboxylic acids, as well as the five alcohols [FL-no: 02.126, 02.154, 02.180, 02.196, and 02.202], and one linear aldehyde [FL-no: 05.152], are expected to be rapidly absorbed from the gastrointestinal tract and to be oxidised to carbon dioxide via the fatty acid pathway followed by the tricarboxylic acid cycle. Alcohols can also be conjugated, especially the branched ones, and excreted via the urine (Browning, 1965; Kamil et al., 1953a). See also Annex II.

Two alcohols and four carboxylic acids resulting from the hydrolysis of the candidate esters [FL-no: 09.358, 09.380, 09.574, 09.642, 09.651, 09.659, 09.661, 09.665, and 09.820] are endogenous in humans (methanol, ethanol, formic acid, acetic acid, propanoic acid, and butyric acid).

The 41 candidate substances would not be expected to saturate available detoxification pathways at current levels of intake from use as flavouring substances.

Therefore the response to step 2 for each of these 41 substances is "Yes" and accordingly they all proceed via the A-side of the Procedure scheme (Annex I).

Step A3.

The 41 candidate substances which have all been assigned to class I have current estimated European daily per capita intakes from less than 0.005 to 7.9 microgram (EFFA, 2001d). These intakes are below the threshold of concern of 1,800 microgram/person/day for class I.

Based on results of the safety evaluation sequence all 41 candidate substances do not pose a safety concern when used at current estimated levels of intake as flavouring substances.

6. Considerations of Combined Intakes from use as Flavouring Substances

On the basis of the reported annual production volumes in Europe (EFFA, 2001d) the total estimated daily per capita intake of the 41 candidate flavouring substances from chemical groups 1

and 2 as flavouring substances is 48 microgram/day, which does not exceed the threshold of concern for a compound belonging to class I of 1,800 microgram per person per day.

The 41 candidate substances are structurally related to 64 flavouring substances (all class I substances) evaluated by JECFA at its 49th session (JECFA, 1999b) where it was noted that, in the unlikely event that all these 64 substances are consumed at the same time, the estimated combined intake (in Europe) was 9,200 microgram per person per day. This exceeds the threshold of concern for a compound belonging to structural class I. However, at the level of exposure resulting from the use as flavourings, all 41 candidate and 64 supporting substances in the combined group are expected to be efficiently metabolised and would not be expected to saturate the metabolic pathways, even if they are ingested together. For these reasons and in the light of toxicological data on candidate and supporting substances (Annex III), the combined intake of these substances would not be expected to be of safety concern

7. Toxicity

7.1. Acute toxicity studies

Data are available for seven [FL-no: 02.126, 02.154, 02.180, 02.196, 09.358, 09.642, and 09.816] of the 41 candidate substances under consideration and for 12 of the structurally related supporting substances [FL-no: 09.010, 09.023, 09.064, 09.096, 09.117, 09.134, 09.182, 09.197, 09.214, 09.246, 09.271 and 09.275] evaluated by JECFA (1999). In addition, information about one related substance was also submitted (isoamyl formate [FL-no: 09.162]). The acute toxicity data are summarised in Annex III, Table III.1.

7.2. Subacute, subchronic, chronic toxicity and carcinogenicity studies

Data are available for one candidate substance [FL-no: 02.196] and for a series of supporting substances [FL-no: 02.001, 02.003, 02.005, 02.008, 02.056, 08.001, 09.004, 09.011, 09.038, 09.044, 09.069, 09.072, 09.075, 09.093, 09.101, 09.106, 09.107, 09.111, 09.117, 09.147, 09.246, and 09.251]. See Annex III, Table III.2

7.3. Developmental / reproductive toxicity studies

Data are available on two candidate substances [FL-no: 02.126 and 02.196] and three supporting substances [FL-no: 09.004, 09.007, and 09.246]. See Annex III, Table III.3

7.4. Genotoxicity studies

For three [FL-no: 02.126, 02.196, and 09.642] out of 41 candidate substances, genotoxicity has been studied *in vitro* in bacteria. With all three candidate substances, negative results were obtained. *In vitro* genotoxicity data are also available for nine supporting substances from the EU Register [FL-no: 09.002, 09.004, 09.005, 09.023, 09.101, 09.117, 09.162, 09.246, and 09.251]. For eight of these nine substances bacterial gene mutation assays have been reported; all with negative results. For two of the nine supporting substances, methyl acetate [FL-no: 09.023] and propyl acetate, [FL-no: 09.002] induction of aneuploidy has been demonstrated in yeast cells, but this effect can be considered to be a threshold effect, which is probably not due to a genotoxic interaction with DNA. Further, it is questionable whether these positive findings with respect to aneuploidy in yeast can be extrapolated to humans. An assay for chromosomal aberrations in mammalian cells *in vitro* with butyl acetate [FL-no: 09.004] was reported to be negative.

There are no *in vivo* data available for the candidate substances. For one supporting substance [FL-no: 02.008] negative results were reported in a micronucleus test in the mouse, while for two other supporting substances [FL-no: 09.004 and 09.023] negative *in vivo* genotoxicity data (SCEs and chromosomal aberrations) have been reported in occupationally exposed people.

At the current level of intake of the only aldehyde of the group, hexadecanal [FL-no: 05.152] of 2.9 microgram per person per day, it is expected that the aldehyde will be oxidised to the corresponding carboxylic acid, hexadecanoic acid (palmitic acid), which is not genotoxic. More detailed information on genotoxicity data is given in Annex III, Table III.4 and III.5.

It is concluded that there is no concern with respect to genotoxicity for the candidate substances dealt with in this flavouring group evaluation.

7.5. Considerations with respect to chirality

All nine candidate flavourings of the present group with chiral centres are esters with the chirality in the alcohol moieties, 2-methylbutanol [FL-no: 09.307, 09.659 - 09.662 and 09.664 - 09.666] and 3,7-dimethyl-1-octanol [FL-no 09.358]. 2-Methylbutyl acetate, which is anticipated to be completely hydrolysed to 2-methylbutanol (and acetic acid) has been evaluated by JECFA (JECFA, 1999b) and found to be of no concern at current level of estimated intake (130 microgram per person per day in Europe), which is far above the estimated combined intake of all eight 2-methylbutyl esters of the present flavouring group evaluation of 9.1 microgram per person per day in Europe. 3,7-Dimethyl-1-octanol has been evaluated by JECFA (JECFA, 1999b) and found to be of no concern at current level of estimated intake (94 microgram per person per day in Europe), which by far exceeds the estimated intake of the candidate ester (less than 0.01 microgram per person per day in Europe).

It was noted, that where toxicity data were available on single flavouring substances, they were consistent with the conclusions in the Flavouring Group Evaluation using the Procedure.

8. Summary and Conclusions

The 41 candidate flavouring substances and the 64 structurally related flavouring substances (supporting substances) are all acyclic aliphatic alcohols, aldehydes or esters.

Nine of the 41 substances in the group posses a chiral centre [FL-no: 09.307, 09.358, 09.659 - 09.662 and 09.664 - 09.666]. In each of these cases the substance has been presented without any indication whether the commercial flavouring substance has dominance of one or the other isomer. The substances have been evaluated irrespective of their chirality. It was noted that 3,7-dimethyl-1-octanol, the alcohol moiety of 3,7-dimethyloctyl acetate [FL-no: 09.358], one of the nine substances with chiral centre, has been evaluated and found to be of no concern at current level of estimated intake by JECFA (JECFA, 1999b). The other eight substances with chiral centres are all esters of 2-methylbutanol. 2-Methylbutyl acetate, which is anticipated to be completely hydrolysed to 2-methylbutanol (and acetic acid), has likewise been evaluated and found to be of no concern at current level of estimated intake by JECFA (JECFA, 1999b).

All 41 flavouring substances belong to structural class I. All of them are expected to participate in common routes of absorption, distribution and metabolism, and exhibit similar toxicological properties. Data for short and medium length linear and branched-chain alcohols and the aldehyde included in the present Flavouring Group Evaluation and general information for this class of chemicals indicate that they are rapidly absorbed from the intestinal tract, metabolised and excreted. Based on published data on compounds structurally related to the esters of the present group of flavourings it can be expected that the 35 esters of the group will be hydrolysed to their corresponding acids and alcohols in humans within a relatively short time.

Although the genotoxicity data are limited, the weight of evidence of *in vitro* and *in vivo* results as well as the chemical structures of 40 out of 41 candidate substances do not raise concerns about genotoxicity for the flavouring substances in this group. The only aldehyde of the candidate group, hexadecanal [FL-no: 05.152], which has a structural alert for genotoxicity, was not studied. However, based on the current levels of intake this substance is expected to be rapidly and completely converted to the corresponding carboxylic acid, hexadecanoic acid (palmitic acid) that is not genotoxic.

It was noted, that where toxicity data were available on single flavouring substances, they were consistent with the conclusions in the present flavouring group evaluation using the Procedure.

The 41 candidate substances have European daily per capita intakes from less than 0.005 to 7.9 microgram/person/day, at current estimated levels of intake, which are below the threshold of concern value for class I of 1,800 microgram/person/day at current estimated levels of intake.

All 41 candidate and 64 supporting substances are expected to be efficiently metabolised and the combined level of intakes of 48 microgram and 9,200 microgram per day, taken together, is not expected to saturate the metabolic pathways.

In conclusion, these 41 flavouring substances per se do not give rise to safety concerns at the current estimated levels of intake from their use as flavourings.

In order to determine whether this conclusion can be applied to the material of commerce it is necessary to consider the toxicological assessment in the light of the available specifications of purity:

- Adequate specifications including complete purity criteria have been provided for 30 materials of commerce [FL-no: 02.126, 02.154, 02.180, 02.196, 02.202, 05.152, 09.307, 09.327, 09.334, 09.358, 09.390, 09.574, 09.579, 09.588, 09.589, 09.592, 09.593, 09.598, 09.602, 09.642, 09.651, 09.659, 09.662, 09.664, 09.677, 09.681, 09.700, 09.813, 09.814, and 09.816] and these are regarded as presenting no safety concern at the current estimated levels of intake.
- The specifications of purity for the remaining 11 substances [FL-no: 09.380, 09.582, 09.587, 09.594, 09.600, 09.660, 09.661, 09.665, 09.666, 09.682, and 09.820] are deficient in one or more of the parameters, and the final evaluation of the material of commerce can not be performed, pending further information on purity.

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 2

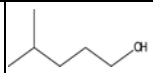
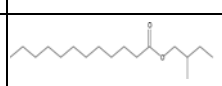
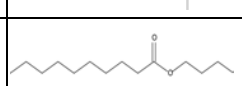
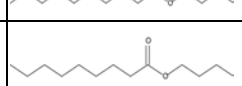
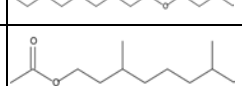
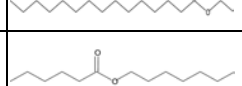
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility in water Solubility in ethanol	Boiling point, °C 3) Melting point, °C	ID test Assay min.	Refrac. Index 4) Spec.gravity 5)	Specification comments
02.126	Tetradecan-1-ol		10314 112-72-1	Liquid $C_{14}H_{30}O$ 214.39	Insoluble in water 1 ml in 1 ml 95 % Ethanol	170 (3 hPa)	IR NMR MS 95 %	1.435-1.441 0.819-0.825	
02.154	Heptadecan-1-ol		- - 1454-85-9	Solid $C_{17}H_{36}O$ 256.47	Insoluble in water 1 ml in 1 ml 95% Ethanol	379 54	IR MS 95 %	n.a. n.a.	
02.180	4-Methylpentan-1-ol		10278 626-89-1	Liquid $C_6H_{14}O$ 102.18	Slightly soluble in water 1 ml in 1 ml 95 % Ethanol	152	IR NMR MS 95 %	1.411-1.417 0.810-0.816	
02.196	Octadecan-1-ol		- - 112-92-5	Solid $C_{18}H_{38}O$ 270.50	Insoluble in water 1 ml in 1 ml 95% Ethanol	210 (20 hPa) 59	IR NMR MS 95 %	n.a. n.a.	
02.202	Pentadecan-1-ol		629-76-5	Solid $C_{15}H_{32}O$ 228.42	Insoluble in water 1 ml in 1 ml 95% Ethanol	133 (1 hPa) 45	IR MS 95 %	1.440-1.446 0.890-0.896	
05.152	Hexadecanal		10336 629-80-1	Solid $C_{16}H_{32}O$ 240.43	Insoluble in water 1 ml in 1 ml 95% Ethanol	144 (1 hPa) 36	IR NMR MS 95 %	n.a. n.a.	
09.307	2-Methylbutyl dodecanoate 1)		10766 55195-19-2	Liquid $C_{17}H_{34}O_2$ 270.45	Insoluble in water 1 ml in 1 ml 95 % Ethanol	308	NMR 95 %	1.434-1.440 0.856-0.862	
09.327	Butyl decanoate		10530 30673-36-0	Liquid $C_{14}H_{28}O_2$ 228.38	Insoluble in water 1 ml in 1 ml 95 % Ethanol	123 (5 hPa)	MS 95 %	1.427-1.433 0.858-0.864	
09.334	Butyl nonanoate		50623-57-9	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble in water 1 ml in 1 ml 95 % Ethanol	123 (3 hPa)	NMR 95 %	1.423-1.429 0.849-0.855	
09.358	3,7-Dimethyloctyl acetate 1)		10899 20780-49-8	Liquid $C_{12}H_{24}O_2$ 200.32	Insoluble in water 1 ml in 1 ml 95 % Ethanol	108 (19 hPa)	IR NMR MS 96 %	1.421-1.429 0.860-0.875	
09.380	Ethyl pentadecanoate		10622 41114-00-5	Liquid $C_{17}H_{34}O_2$ 270.46	Insoluble in water 1 ml in 1 ml 95% Ethanol	173 (20 hPa) 12	NMR 95 %	0.858-0.866	RI 2)
09.390	Heptyl hexanoate		10666 6976-72-3	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble in water 1 ml in 1 ml 95 % Ethanol	259	IR 95 %	1.421-1.427 0.859-0.865	

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 2, continued

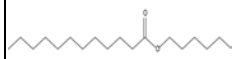
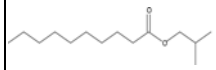
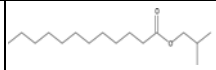
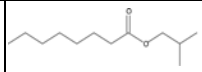
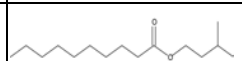
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility in water Solubility in ethanol	Boiling point, °C 3) Melting point, °C	ID test Assay min.	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.574	Hexadec-1-yl acetate		 629-70-9	Solid $C_{12}H_{36}O_2$ 284.48	Insoluble in water 1 ml in 1 ml 95 % Ethanol	200 (20 hPa) 24	IR NMR MS 95 %	1.439-1.445 0.856-0.862	
09.579	Hexyl dodecanoate		 34316-64-8	Liquid $C_{18}H_{36}O_2$ 284.48	Insoluble in water 1 ml in 1 ml 95 % Ethanol	130 (1 hPa)	NMR 95 %	1.436-1.442 0.855-0.860	
09.582	Hexyl tetradecanoate		 42231-99-2	Liquid $C_{20}H_{40}O_2$ 312.54	Insoluble in water 1 ml in 1 ml 95% Ethanol	215 (23 hPa)	NMR 95 %		RI, SG 2)
09.587	Isobutyl decanoate		10707 30673-38-2	Liquid $C_{14}H_{28}O_2$ 288.38	Insoluble in water 1 ml in 1 ml 95 % Ethanol	272	NMR 95 %		RI, SG 2)
09.588	Isobutyl dodecanoate		10708 37811-72-6	Liquid $C_{16}H_{32}O_2$ 256.43	Insoluble in water 1 ml in 1 ml 95 % Ethanol	330	NMR 95 %	1.428-1.436 0.852-0.861	
09.589	Isobutyl hexadecanoate		10715 110-34-9	Solid $C_{20}H_{40}O_2$ 312.53	Insoluble in water 1 ml in 1 ml 95% Ethanol	207 (20 hPa) 20	IR NMR 95 %	n.a. n.a.	
09.592	Isobutyl octadecanoate		- - 646-13-9	Solid $C_{22}H_{44}O_2$ 340.59	Insoluble in water 1 ml in 1 ml 95 %	223 (20 hPa) 29	NMR 95 %	n.a. n.a.	
09.593	Isobutyl octanoate		10714 5461-06-3	Liquid $C_{12}H_{24}O_2$ 200.32	Insoluble in water 1 ml in 1 ml 95 % Ethanol	226	NMR 95 %	1.416-1.426 0.852-0.864	
09.594	Isobutyl tetradecanoate		10712 25263-97-2	Solid $C_{18}H_{36}O_2$ 284.48	Insoluble in water 1 ml in 1 ml 95% Ethanol	330 47	NMR 95 %	n.a. n.a.	
09.598	Isopentyl decanoate		 2306-91-4	Liquid $C_{15}H_{30}O_2$ 242.40	Insoluble in water 1 ml in 1 ml 95 % Ethanol	124 (4 hPa)	NMR 98 %	1.428-1.435 0.848-0.865	
09.600	Isopentyl hexadecanoate		10723 81974-61-0	Liquid $C_{21}H_{42}O_2$ 326.56	insoluble in water 1 ml in 1 ml 95% ethanol	365 12	 95 %	1.429-1.435 (50°C)	ID, SG 2)
09.602	Isopentyl tetradecanoate		10722 62488-24-8	Solid $C_{19}H_{38}O_2$ 298.51	Insoluble in water 1 ml in 1 ml 95% Ethanol	342 58	NMR 95 %	n.a. n.a.	

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 2, continued

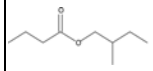
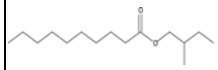
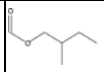
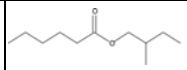
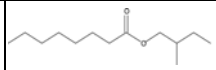
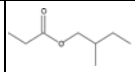
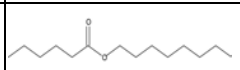
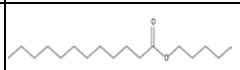
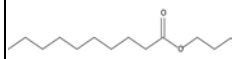
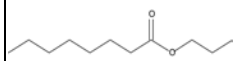
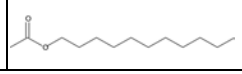
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility in water Solubility in ethanol	Boiling point, °C 3) Melting point, °C	ID test Assay min.	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.642	Methyl formate		10795 107-31-3	Liquid $C_2H_4O_2$ 60.05	slightly soluble in water 1 ml in 1 ml 95% Ethanol	32	IR NMR MS 99 %	1.341-1.346 0.960-0.985	
09.651	Methyl octadecanoate		10849 112-61-8	Solid $C_{19}H_{38}O_2$ 298.51	Insoluble in water 1 ml in 1 ml 95% Ethanol	210 (20 hPa) 38	IR NMR MS 95 %	1.438-1.444 0.847-0.853	
09.659	2-Methylbutyl butyrate 1)		51115-64-1	Liquid $C_9H_{18}O_2$ 158.24	Insoluble inwater 1 ml in 1 ml 95% Ethanol	178	NMR 95 %	1.408-1.414 0.862-0,868	
09.660	2-Methylbutyl decanoate 1)		10765 55195-23-8	Liquid $C_{15}H_{30}O_2$ 242.4	Insoluble in water 1 ml in 1 ml 95 % Ethanol	151 (13 hPa)	NMR 95 %	1.430-1.436	SG 2)
09.661	2-Methylbutyl formate 1)		35073-27-9	Liquid $C_6H_{12}O_2$ 116.16	Slightly soluble in water 1 ml in 1 ml 95% Ethanol	45 (0.01 hPa)	NMR 95 %		RI, SG 2)
09.662	2-Methylbutyl hexanoate 1)		10768 2601-13-0	Liquid $C_{11}H_{22}O_2$ 186.29	Insoluble in water 1 ml in 1 ml 95 % Ethanol	213	MS 95 %	1.417-1.423 0.856-0.862	
09.664	2-Methylbutyl octanoate 1)		10776 67121-39-5	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble in water 1 ml in 1 ml 95 % Ethanol	252 (97 hPa)	MS 95 %	1.424-1.430 0.857-0.863	
09.665	2-Methylbutyl propionate 1)		10778 2438-20-2	Liquid $C_8H_{16}O_2$ 144.21	Slightly soluble in water 1 ml in 1 ml 95% Ethanol	157	MS 95 %	1.404-1.410	SG 2)
09.666	2-Methylbutyl tetradecanoate 1)		10774 93805-23-3	Liquid $C_{19}H_{38}O_2$ 298.51	Insoluble in water 1 ml in 1 ml 95% Ethanol	197 (13 hPa)	NMR 95 %	1.438-1.444	SG 2)
09.677	Octyl hexanoate		10865 4887-30-3	Liquid $C_{14}H_{28}O_2$ 228.38	Insoluble in water 1 ml in 1 ml 95 % Ethanol	99 (1 hPa)	IR NMR 95 %	1.420-1.426 0.850-0.856	
09.681	Pentyl dodecanoate		5350-03-8	Solid $C_{17}H_{34}O_2$ 270.46	Insoluble in water 1 ml in 1 ml 95 % Ethanol	325 50	NMR 95 %	n.a. n.a.	
09.682	Pentyl hexadecanoate		- - 31148-31-9	Solid $C_{21}H_{42}O_2$ 326.56	Insoluble in water 1 ml in 1 ml 95% Ethanol	372 95	95 %	1.429-1.435 (50°C) n.a.	ID 2)

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 2, continued

FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility in water Solubility in ethanol	Boiling point, °C 3) Melting point, °C	ID test Assay min.	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.700	Propyl decanoate		 30673-60-0	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble in water 1 ml in 1 ml 95 % Ethanol	131 (15 hPa)	NMR 95 %	1.418-1.433 0.850-0.865	SG range
09.813	Propyl dodecanoate		 3681-78-5	Liquid $C_{15}H_{30}O_2$ 242.40	Insoluble in water 1 ml in 1 ml 95 % Ethanol	291	NMR 95 %	1.430-1.436 0.859-0.865	
09.814	Propyl hexadecanoate		10893 2239-78-3	Solid $C_{19}H_{38}O_2$ 298.51	Insoluble in water 1 ml in 1 ml 95% Ethanol	209 (29 hPa) 21	IR NMR MS 95 %	1.436-1.442 0.827-0.833	
09.816	Propyl octanoate		10892 624-13-5	Liquid $C_{11}H_{22}O_2$ 186.29	Insoluble in water 1 ml in 1 ml 95 % Ethanol	226	IR 95 %	1.418-1.424 0.861-0.867	
09.820	Undecyl acetate		10906 1731-81-3	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble in water 1 ml in 1 ml 95 % Ethanol	142 (20 hPa)	IR NMR MS 95 %	 0.858-0.864	RI 2)

1) Stereoisomeric purity not specified

2) A: missing minimum assay value, BP: missing boiling point, ID: missing identification test, RI: missing refractive index, SG: missing specific gravity

3) At 1013.25 hPa, if not otherwise stated

4) At 20°C, if not otherwise stated

5) At 25°C, if not otherwise stated

Table 2: Summary of Safety Evaluation Results

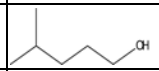
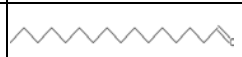
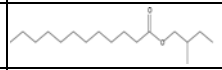
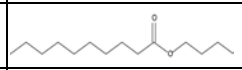
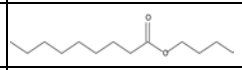
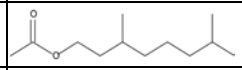
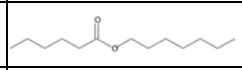
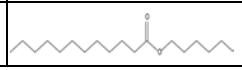
FL-no	EU Register name	Structural formula	MSDI 1) (µg/person/day)	Class 2)	Evaluation procedure path 3)	Conclusion on the named compound 4) or 5)	Conclusion on the material of commerce 6), 7), or 8)
02.126	Tetradecan-1-ol		0.07	Class I	A3: Intake below threshold	No safety concern 4)	6)
02.154	Heptadecan-1-ol		<0.005	Class I	A3: Intake below threshold	No safety concern 4)	6)
02.180	4-Methylpentan-1-ol		0.01	Class I	A3: Intake below threshold	No safety concern 4)	6)
02.196	Octadecan-1-ol		0.14	Class I	A3: Intake below threshold	No safety concern 4)	6)
02.202	Pentadecan-1-ol		0.03	Class I	A3: Intake below threshold	No safety concern 4)	6)
05.152	Hexadecanal		2.9	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.307	2-Methylbutyl dodecanoate		0.57	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.327	Butyl decanoate		7.9	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.334	Butyl nonanoate		1.6	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.358	3,7-Dimethyloctyl acetate		<0.005	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.380	Ethyl pentadecanoate		0.01	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.390	Heptyl hexanoate		0.03	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.574	Hexadec-1-yl acetate		0.01	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.579	Hexyl dodecanoate		0.29	Class I	A3: Intake below threshold	No safety concern 4)	6)

Table 2: Summary of Safety Evaluation Results, continued

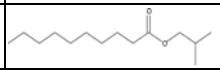
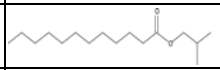
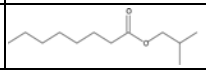
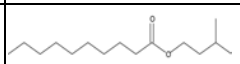
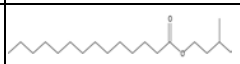
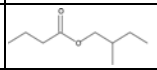
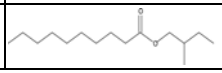
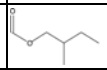
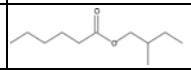
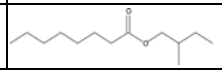
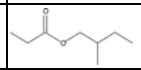
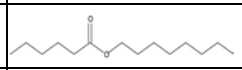
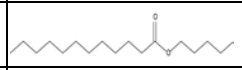
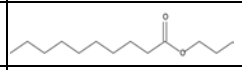
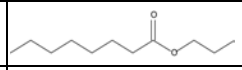
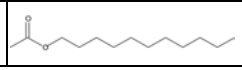
FL-no	EU Register name	Structural formula	MSDI 1) (µg/person/day)	Class 2)	Evaluation procedure path 3)	Conclusion on the named compound 4) or 5)	Conclusion on the material of commerce 6), 7), or 8)
09.582	Hexyl tetradecanoate		0.71	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.587	Isobutyl decanoate		3.6	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.588	Isobutyl dodecanoate		0.71	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.589	Isobutyl hexadecanoate		0.29	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.592	Isobutyl octadecanoate		<0.005	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.593	Isobutyl octanoate		4.3	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.594	Isobutyl tetradecanoate		2.1	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.598	Isopentyl decanoate		5.3	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.600	Isopentyl hexadecanoate		0.14	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.602	Isopentyl tetradecanoate		0.29	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.642	Methyl formate		1.1	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.651	Methyl octadecanoate		0.86	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.659	2-Methylbutyl butyrate		2.4	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.660	2-Methylbutyl decanoate		1.0	Class I	A3: Intake below threshold	No safety concern 4)	7)

Table 2: Summary of Safety Evaluation Results, continued

FL-no	EU Register name	Structural formula	MSDI 1) (µg/person/day)	Class 2)	Evaluation procedure path 3)	Conclusion on the named compound 4) or 5)	Conclusion on the material of commerce 6), 7), or 8)
09.661	2-Methylbutyl formate		1.1	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.662	2-Methylbutyl hexanoate		0.57	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.664	2-Methylbutyl octanoate		0.43	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.665	2-Methylbutyl propionate		2.9	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.666	2-Methylbutyl tetradecanoate		0.14	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.677	Octyl hexanoate		0.71	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.681	Pentyl dodecanoate		<0.005	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.682	Pentyl hexadecanoate		<0.005	Class I	A3: Intake below threshold	No safety concern 4)	7)
09.700	Propyl decanoate		1.6	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.813	Propyl dodecanoate		0.71	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.814	Propyl hexadecanoate		0.86	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.816	Propyl octanoate		3.0	Class I	A3: Intake below threshold	No safety concern 4)	6)
09.820	Undecyl acetate		<0.005	Class I	A3: Intake below threshold	No safety concern 4)	7)

1) MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/person/day

2) Threshold of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person/day

3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.

4) No safety concern at estimated current level of intake of the named compound.

5) Data must be available on the substance or closely related substances to perform a safety evaluation.

6) No safety concern at estimated current level of intake of the material of commerce meeting the specification of Table 1

7) Tentatively regarded as presenting no safety concern pending further information on the purity of the material of commerce.

8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.

Table 3: Supporting Substances Summary

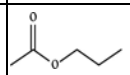
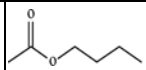
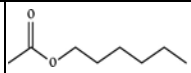
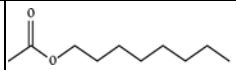
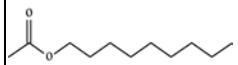
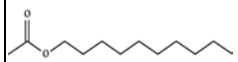
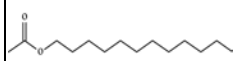
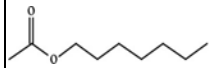
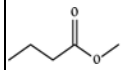
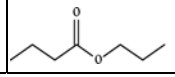
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no	Specification available	MSDI (EU) 1) (μg/person/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.002	Propyl acetate		2925 192 109-60-4	126	JECFA specification d)	180	- No safety concern a) Category A b)	
09.004	Butyl acetate		2174 194 123-86-4	127	JECFA specification d)	1,200	- No safety concern a) Category A b)	
09.005	Isobutyl acetate		2175 195 110-19-0	137	JECFA specification d)	1,200	- No safety concern a) Category A b)	
09.006	Hexyl acetate		2565 196 142-92-7	128	JECFA specification d)	3,200	- No safety concern a) Category A b)	Metabolites endogenous
09.007	Octyl acetate		2806 197 112-14-1	130	JECFA specification d)	83	- No safety concern a) Category A b)	
09.008	Nonyl acetate		2788 198 143-13-5	131	JECFA specification d)	6,6	- No safety concern a) Category A b)	
09.009	Decyl acetate		2367 199 112-17-4	132	JECFA specification d)	7,3	- No safety concern a) Category A b)	
09.010	Dodecyl acetate		2616 200 112-66-3	133	JECFA specification d)	9,3	- No safety concern a) Category A b)	
09.022	Heptyl acetate		2547 212 112-06-1	129	JECFA specification d)	56	- No safety concern a) Category A b)	
09.023	Methyl acetate		2676 213 79-20-9	125	JECFA specification d)	460	- No safety concern a) Category A b)	
09.038	Methyl butyrate		2693 263 623-42-7	149	JECFA specification d)	220	Category 1 c) No safety concern a) Category A b)	
09.040	Propyl butyrate		2934 266 105-66-8	150	JECFA specification d)	75	Category 1 c) No safety concern a) Category A b)	

Table 3: Supporting Substances Summary, continued

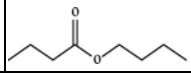
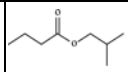
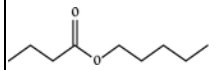
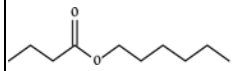
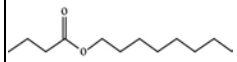
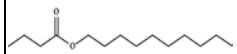
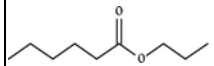
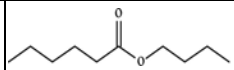
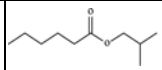
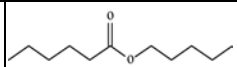
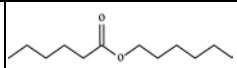
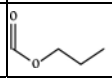
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no	Specification available	MSDI (EU) 1) (μg/person/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.042	Butyl butyrate		2186 268 109-21-7	151	JECFA specification d)	390	- No safety concern a) Category A b)	
09.043	Isobutyl butyrate		2187 269 539-90-2	158	JECFA specification d)	47	- No safety concern a) Category A b)	
09.044	Pentyl butyrate		2059 270 540-18-1	152	JECFA specification d)	450	Category 1 c) No safety concern a) Category A b)	
09.045	Hexyl butyrate		2568 271 2639-63-6	153	JECFA specification d)	110	Category 1 c) No safety concern a) Category A b)	
09.046	Octyl butyrate		2807 272 110-39-4	155	Tentative JECFA spec. d)	16	Category 1 c) No safety concern a) Category A b)	
09.047	Decyl butyrate		2368 273 5454-09-1	156	Tentative JECFA spec. d)	0	Category 1 c) No safety concern a) Category A b)	
09.061	Propyl hexanoate		2949 311 626-77-7	161	JECFA specification d)	14	- No safety concern a) Category A b)	
09.063	Butyl hexanoate		2201 313 626-82-4	162	JECFA specification d)	15	- No safety concern a) Category A b)	
09.064	Isobutyl hexanoate		2202 314 105-79-3	166	JECFA specification d)	6,1	- No safety concern a) Category A b)	
09.065	Pentyl hexanoate		2074 315 540-07-8	163	JECFA specification d)	8,7	- No safety concern a) Category A b)	
09.066	Hexyl hexanoate		2572 316 6378-65-0	164	JECFA specification d)	150	- No safety concern a) Category A b)	
09.073	Propyl formate		2943 340 110-74-7	117	JECFA specification d)	5	- No safety concern a) Category A b)	

Table 3: Supporting Substances Summary, continued

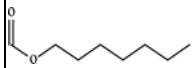
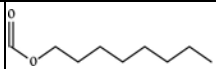
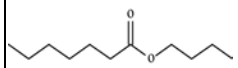
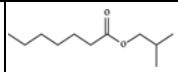
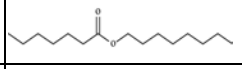
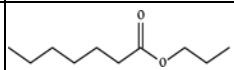
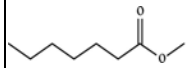
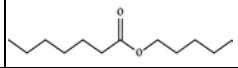
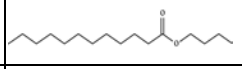
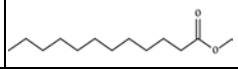
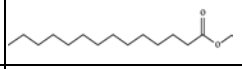
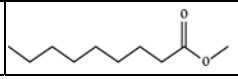
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no	Specification available	MSDI (EU) 1) (μg/person/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.074	Heptyl formate		2552 341 112-23-2	121	Tentative JECFA spec. d)	0	- No safety concern a) Category A b)	
09.075	Octyl formate		2809 342 112-32-3	122	JECFA specification d)	0,14	- No safety concern a) Category A b)	
09.091	Butyl heptanoate		2199 363 5454-28-4	169	Tentative JECFA spec. d)	0	- No safety concern a) Category A b)	
09.092	Isobutyl heptanoate		2200 364 7779-80-8	172	Tentative JECFA spec. d)	0,01	- No safety concern a) Category A b)	
09.094	Octyl heptanoate		2810 366 5132-75-2	171	Tentative JECFA spec. d)	0,21	- No safety concern a) Category B b)	
09.095	Propyl heptanoate		2948 367 7778-87-2	168	Tentative JECFA spec. d)	0,14	- No safety concern a) Category A b)	
09.096	Methyl heptanoate		2705 368 106-73-0	167	JECFA specification d)	5,7	- No safety concern a) Category A b)	
09.098	Pentyl heptanoate		2073 370 7493-82-5	170	JECFA specification d)	0,61	- No safety concern a) Category B b)	
09.100	Butyl dodecanoate		2206 376 106-18-3	181	JECFA specification d)	0	Category 1 c) No safety concern a) Category A b)	
09.101	Methyl dodecanoate		2715 377 111-82-0	180	JECFA specification d)	5,1	Category 1 c) No safety concern a) Category A b)	
09.106	Methyl tetradecanoate		2722 387 124-10-7	183	JECFA specification d)	62	Category 1 c) No safety concern a) Category B b)	
09.108	Methyl nonanoate		2724 389 1731-84-6	179	JECFA specification d)	0,86	Category 1 c) No safety concern a) Category A b)	

Table 3: Supporting Substances Summary, continued

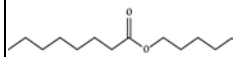
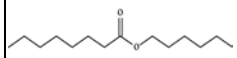
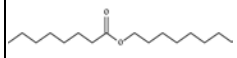
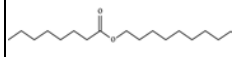
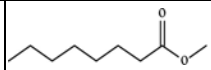
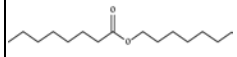
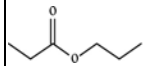
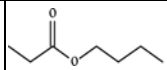
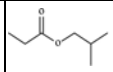
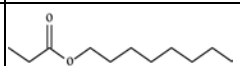
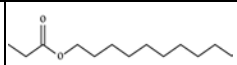
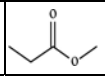
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no	Specification available	MSDI (EU) 1) (μg/person/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.112	Pentyl octanoate		2079 393 638-25-5	174	JECFA specification d)	3,4	Category 1 c) No safety concern a) Category A b)	
09.113	Hexyl octanoate		2575 394 1117-55-1	175	JECFA specification d)	1,3	Category 1 c) No safety concern a) Category B b)	
09.114	Octyl octanoate		2811 395 2306-88-9	177	Tentative JECFA spec. d)	0,03	Category 1 c) No safety concern a) Category B b)	
09.115	Nonyl octanoate		2790 396 7786-48-3	178	Tentative JECFA spec. d)	0,14	Category 1 c) No safety concern a) Category B b)	
09.117	Methyl octanoate		2728 398 111-11-5	173	JECFA specification d)	9,7	Category 1 c) No safety concern a) Category A b)	
09.118	Heptyl octanoate		2553 399 4265-97-8	176	Tentative JECFA spec. d)	0,71	Category 1 c) No safety concern a) Category B b)	
09.122	Propyl propionate		2958 403 106-36-5	142	JECFA specification d)	9,6	- No safety concern a) Category A b)	
09.124	Butyl propionate		2211 405 590-01-2	143	JECFA specification d)	10	- No safety concern a) Category A b)	
09.125	Isobutyl propionate		2212 406 540-42-1	148	JECFA specification d)	12	- No safety concern a) Category A b)	
09.126	Octyl propionate		2813 407 142-60-9	145	JECFA specification d)	0	- No safety concern a) Category A b)	
09.127	Decyl propionate		2369 408 5454-19-3	146	JECFA specification d)	0	- No safety concern a) Category A b)	
09.134	Methyl propionate		2742 415 554-12-1	141	JECFA specification d)	9,3	- No safety concern a) Category A b)	

Table 3: Supporting Substances Summary, continued

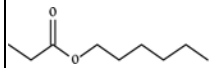
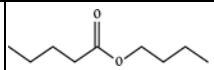
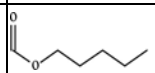
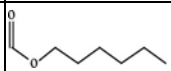
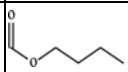
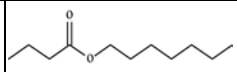
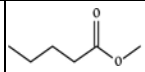
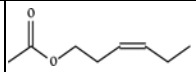
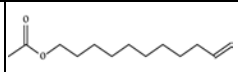
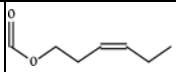
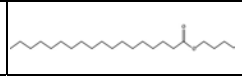
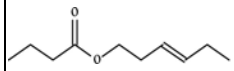
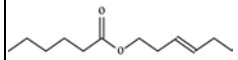
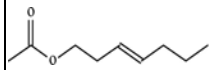
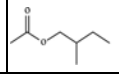
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no	Specification available	MSDI (EU) 1) (μg/person/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.139	Hexyl propionate		2576 420 2445-76-3	144	JECFA specification d)	5,7	- No safety concern a) Category A b)	
09.148	Butyl valerate		2217 466 591-68-4	160	JECFA specification d)	3,7	Category 1 c) No safety concern a) Category A b)	
09.159	Pentyl formate		2068 497 638-49-3	119	JECFA specification d)	29	- No safety concern a) Category A b)	
09.161	Hexyl formate		2570 499 629-33-4	120	JECFA specification d)	8,7	- No safety concern a) Category A b)	
09.163	Butyl formate		2196 501 592-84-7	118	JECFA specification d)	21	- No safety concern a) Category A b)	
09.164	Isobutyl formate		2197 502 542-55-2	124	JECFA specification d)	4,7	- No safety concern a) Category A b)	
09.166	Heptyl butyrate		2549 504 5870-93-9	154	Tentative JECFA spec. d)	6	Category 1 c) No safety concern a) Category A b)	
09.182	Methyl valerate		2752 588 624-24-8	159	JECFA specification d)	30	Category 1 c) No safety concern a) Category A b)	
09.197	Hex-3(cis)-enyl acetate		3171 644 3681-71-8	134	JECFA specification d)	640	- No safety concern a) Category B b)	
09.214	Undec-10-enyl acetate		3096 2062 112-19-6	136	JECFA specification d)	0,83	- No safety concern a) Category B b)	
09.240	Hex-3(cis)-enyl formate		3353 2153 33467-73-1	123	JECFA specification d)	43	- No safety concern a) Category B b)	
09.246	Butyl octadecanoate		2214 2189 123-95-5	184	Tentative JECFA spec. d)	5,1	- No safety concern a) Deleted	

Table 3: Supporting Substances Summary, continued

FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no	Specification available	MSDI (EU) 1) (µg/person/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.270	Hex-3-enyl butyrate		3402 11859 16491-36-4	157	JECFA specification d)	160	- No safety concern a) -	
09.271	Hex-3-enyl hexanoate		3403 11779 31501-11-8	165	Tentative JECFA spec. d)	42	- No safety concern a) -	
09.275	Hept-3(trans)-enyl acetate		3493 10662 1576-77-8	135	JECFA specification d)	0,24	- No safety concern a) -	
09.286	2-Methylbutyl acetate		3644 10762 624-41-9	138	JECFA specification d)	130	- No safety concern a) -	

1) MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/person/day

2) Category 1: Considered safe in use, Category 2: Temporarily considered safe in use, Category 3: Insufficient data to provide assurance of safety in use, Category 4: Not acceptable due to evidence of toxicity

3) No safety concern at estimated current levels of intake

4) Category A: Flavouring substances, which may be used in foodstuffs, Category B: Flavoruing substances which can be used provisionally in foodstuffs

a) (JECFA, 1999b)

b) (CoE, 1992)

c) (SCF, 1995)

d) (JECFA, 1997b)

Annex I: Procedure for the Safety Evaluation

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation EC No 1565/2000 (EC, 2000), named the "Procedure", is shown in schematic form in Figure I.1. The Procedure is based on the opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999), which is derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b).

The Procedure is a stepwise approach that integrates information on intake from current uses, structure-activity relationships, metabolism and, when needed, toxicity. One of the key elements in the procedure is the subdivision of flavourings into three structural classes (I, II, III) for which thresholds of concern (human exposure thresholds) that are not considered to present a safety concern have been specified.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous, but are not suggestive of toxicity. Class III comprises flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The thresholds of concern for these structural classes of 1800, 540 or 90 μg/person/day, respectively are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996a).

In Step 1 of the Procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions:

- can the flavourings be predicted to be metabolised to innocuous products[1] (Step 2)?
- do their exposures exceed the threshold of concern for the structural class (Step A3 and B3)?
- are the flavourings or their metabolites endogenous[2] (Step A4)?
- does a NOEL exist on the flavourings or on structurally related substances (Step A5 and B4)?

In addition to the data provided for the flavouring substances to be evaluated (candidate substances), toxicological background information available for compounds structurally related to the candidate substances is considered (supporting substances), in order to assure that these data are consistent with the results obtained after application of the Procedure.

The Procedure is not to be applied to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches if data on specific flavourings warranted such actions.

[1] *"Innocuous metabolic products": Products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent" (JECFA, 1997a).*

[2] *"Endogenous substances": Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997a).*

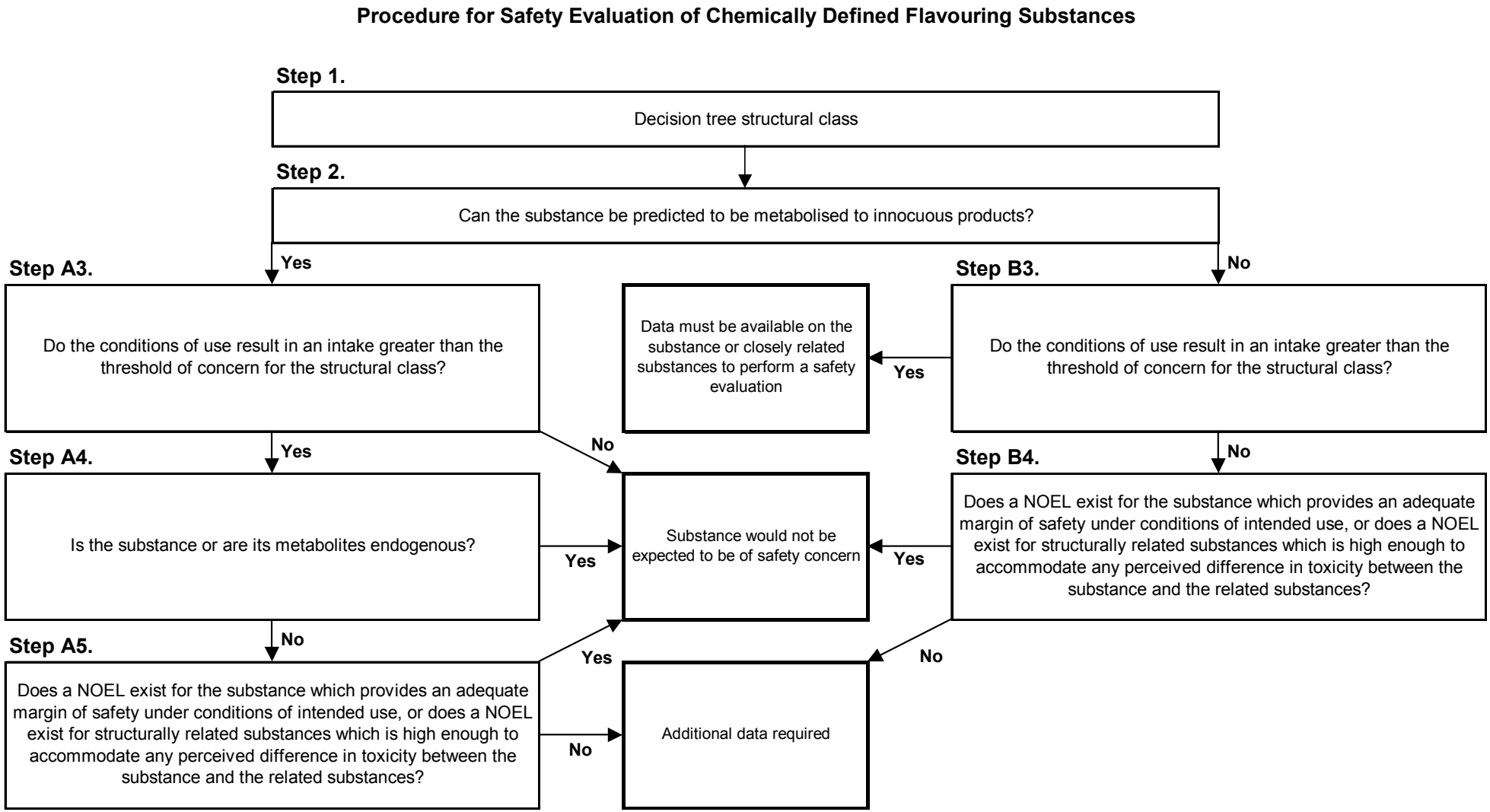


Figure I.1 Procedure for Safety evaluation of Chemically Defined Flavouring Substances

Annex II: Metabolism

II.1. Absorption, distribution and excretion

Data for short- and medium-length linear alcohols, aldehydes and esters (and their component alcohols and carboxylic acids) included in this evaluation, and more general information for this class of chemicals indicate that they are rapidly absorbed from the gastrointestinal tract (JECFA, 1999b). Information on distribution and excretion of these compounds has not been submitted, but as these flavouring substances can be expected to be extensively metabolised to substances that are easily excreted (see below).

The relevant and specific information available on the absorption, distribution and excretion of the flavouring substances included in this monograph or chemical analogues follows:

Methyl formate [FL-no: 09.642]

Methyl formate is expected to be hydrolysed in the gastrointestinal (GI) tract to methanol and formic acid (see below). Methanol and formic acid are rapidly absorbed from the GI tract of man (Lund, 1948; Malorny, 1969a). The biological half-lives of formic acid and methanol in man following ingestion are approximately 45 minutes (Malorny, 1969a) and 7 hours (estimated from data in (Leaf & Zatman, 1952)), respectively. In comparison the corresponding biological half-lives of formic acid in rats and guinea pigs are approximately 12 minutes and 22 minutes, respectively (Malorny, 1969b).

2-Methylbutan-1-ol [FL-no: 02.076]

Small amounts of the amyl alcohols pentan-1-ol [FL-no: 02.040], 2-methylbutan-1-ol [FL-no: 02.076], and 3-methylbutan-1-ol [FL-no: 02.003] were excreted via expired air (0.088 to 5.6% of total dose) or urine (0.27 to 2.0% of total dose) following 1 g/kg dose i.p. injection to rats (Haggard et al., 1945). The maximum blood alcohol concentrations ranged from 14 to 55 mg/100 ml and were no longer detectable in the blood after 4 to 9 hours. Rapid metabolism probably accounted for the low blood alcohol levels reported. The closely related branched-chain aliphatic candidate chemical alcohol, 4-methylpentan-1-ol [FL-no: 02.180], would be expected to follow a similar pattern of absorption, distribution, metabolism and excretion.

The branched chain candidate chemical ester, 2-methylbutyl formate [09.661] would be expected to follow a very similar pattern of absorption, distribution and excretion as described for methyl formate [FL-no: 09.642] and 2-methylbutan-1-ol [FL-no: 02.076].

Hexadecan-1-ol [FL-no: 02.009]

Data for the C16 aliphatic alcohol, hexadecan-1-ol (cetyl alcohol), indicate that of the 34% total absorbed (recovered in thoracic duct lymph, carcass, liver, expired CO_2, and urine) of a dose in corn oil administered by oral gavage to male Sprague-Dawley rats, 75% was found in the thoracic duct lymph after 24 hours and that 85% of this material had been converted to fatty acid, presumed to be palmitic acid (Baxter et al., 1967). Another study corroborates this result in that cetyl alcohol was well absorbed (63 to 96%, based on the difference between amount administrated and amount recovered from the intestinal tract and faeces) when fed to rats. From 31 to 64% of the absorbed material was recovered from the thoracic lymph lipids. About 15% of this amount was present as unchanged cetyl alcohol. The remainder had been oxidised to palmitic acid and subsequently incorporated into triglycerides and phospholipids. The main part of this oxidation process took

place during the passage of the lipids through the intestinal mucosa cells (Blomstrand & Rumpf, 1954). The C14 and C15 linear-chain aliphatic candidate chemical alcohols, i.e. tetradecan-1-ol [FL-no: 02.126] and pentadecan-1-ol [FL-no: 02.202], would be expected to follow a similar pattern of absorption, distribution and excretion as the closely related C16 linear-chain aliphatic alcohol, hexadecan-1-ol.

II.2. Biotransformation

A general discussion of the biotransformation of esters of aliphatic linear or branched chain alcohols and linear aliphatic acids and their alcohol and acid moieties, as well as specific discussions of the metabolic pathways for propyl alcohol [FL-no: 02.002], 2-ethylbutyl alcohol [FL-no: 02.043], isobutyl alcohol [FL-no: 02.001], isoamyl alcohol [FL-no: 02.003], isobutyraldehyde [FL-no: 05.004], acetaldehyde [FL-no: 05.001], isobutyric acid [FL-no: 08.006], isovaleric acid [FL-no: 08.008], and 2-methylbutyric acid [FL-no: 08.046] are provided by JECFA (JECFA, 1999b). These discussions and conclusions apply equally well to the candidate substances as they do to the supporting substances.

The following additional discussion on the metabolism of the short and medium-length linear or branched aliphatic alcohols, aldehydes, esters of linear carboxylic acids, and linear or branched chain-carboxylic acids is structured according to the general metabolic reactions that have been demonstrated for these or similar chemicals. The likelihood that the candidate substances undergo these metabolic reactions depends on their chain length and degree of branching and functional groups. It is likely that multiple metabolic reactions will occur for some substances. The probable metabolic reactions are the following:

II.2.1. Ester hydrolysis
II.2.2. Oxidation of alcohols and aldehydes to acids
II.2.3. Reduction of aldehydes to alcohols
II.2.4. Metabolism to glucuronides and sulphates
II.2.5. beta-Oxidation of carboxylic acids
II.2.6. omega-Oxidation of carboxylic acids
II.2.7. Other biotransformation reactions

II.2.1. Ester hydrolysis

The esters included in this monograph are expected to be hydrolysed enzymatically to carboxylic acids and alcohols via carboxylesterases found in most tissues throughout the body, the most important of which are the beta-esterases. beta-Esterases have been demonstrated in almost all mammalian tissues with the highest concentration of esterase activity towards simple aliphatic and aromatic substrates invariably localised in the liver (Heymann, 1980).

In a study of the influence of the alkyl (C1-C7) and acyl chain length (C1-C7) of aliphatic esters on kinetic parameters of rat liver carboxylesterase, it was found that an elongation of the alcohol chain up to C4 leads to a linear increase of the Km values approaching a plateau from C4 to C7. A variation on the length of the acyl part had no significant influence on Km (Arndt & Krisch, 1973). In a later study with similar substrates, other authors (Junge & Heymann, 1979) found that short chain unbranched aliphatic esters are good substrates for pig-liver carboxyl esterase with respect to reaction rates and affinity. However, different isoenzymes showed striking differences in the hydrolysis rates. In the case of variation of the acyl chain, isoenzyme V had an optimum for the C5

compound (methyl pentanoate), while with acetate esters of varying chain length of the alcohol moiety, this isoenzyme exhibited a minimum activity with butyl and pentyl acetate. In contrast, the activity of isoenzyme I increased constantly with increasing chain length of both, the acyl and the alcohol moieties. The authors concluded that it appears reasonable to assume a cooperative and complementary function, which is fulfilled by the different substrate specificities of the esterase isoenzymes.

While no hydrolysis data have been provided for the esters of the present group of flavourings, there are in vitro hydrolysis data for some structurally related esters. Structurally related esters were shown to be hydrolysed rather slowly in artificial gastric juice (half-life T1/2 146-770 min) (Longland et al., 1977; Gangolli & Shilling, 1968). Hydrolysis in artificial pancreatic juice/pancreatin was found to be faster than in artificial gastric juice (Gangolli & Shilling, 1968; Longland et al., 1977; Leegwater & Straten, 1974; Grundschober, 1977). However, there is a variation in the degree of hydrolysis between different structurally related esters. Hydrolysis by artificial pancreatic juice was rather fast for some esters (T1/2 of ethylbutyrate, isoamyl butyrate, ethyl hexanoate, ethyl heptanoate, ethyl nonanoate, and ethyl laurate were 6, 11, 3, 10, 6, and 6 min, respectively) and relatively slow for other esters (T1/2 of butyl acetate and isoamyl hexanoate were 66 and 38 min., respectively). Rat liver homogenate and small intestinal mucosa preparation were found to be much more efficient in hydrolysing esters. While half lives of butyl acetate were 491 and 108 sec for hydrolysis by liver homogenate and intestinal mucosa preparation, respectively, half lives of isoamyl butyrate, ethyl hexanoate, and ethyl heptanoate were less than 1 second in liver homogenate or small intestinal mucosa preparation (Longland et al., 1977).

Based on these data on substances structurally related to the esters included in this evaluation it can be expected that the 35 esters included in this evaluation will be hydrolysed to their corresponding acids and alcohols in humans within a relatively short time. The expected hydrolysis products for the 35 esters, and their evaluation status when used as flavouring substances, are shown in Table 2b.

II.2.2. Oxidation of alcohols and aldehydes to acids

Linear and branched chain saturated alcohols and aldehydes are oxidised to corresponding carboxylic acids by high capacity NAD+/NADH-dependent enzymes (Parkinson, 1996a; Feron et al., 1991).

Alcohol dehydrogenase (ADH) enzymes are cytosolic enzymes that are primarily responsible for the oxidation of alcohols to their corresponding aldehydes. Alcohols also can be oxidised to aldehydes by non-ADH enzymes present in the microsomes and peroxisomes, but these are generally quantitatively less important than ADH for ethanol oxidation. Aldehyde dehydrogenases (ALDH) oxidise aldehydes to their corresponding carboxylic acids. Of the several ALDH enzymes involved in the oxidation of aldehydes, Class I ALDH enzymes are responsible for the oxidation of the widest variety of aldehydes (Parkinson, 1996a) and would be expected to be responsible for the oxidation of the candidate substances. Branched-chain aliphatic alcohols and aldehydes are also good substrates for ADH and ALDH (Hedlund & Kiessling, 1969a; Albro, 1975).

II.2.3. Reduction of aldehydes to alcohols

Aldehydes also may be reduced to alcohols, but reduction has a minor overall impact on aldehyde metabolism. Reduction is a reversible reaction, while oxidation is irreversible and the Km of ALDH is substantially lower (higher affinity) than the Km of the reductases for the aldehydes (Sladek et al., 1989, as cited in (Feron et al., 1991)).

II.2.4. Metabolism to glucuronides and sulphates

Hydroxyl and carboxyl functional groups are sensitive to conjugation reactions with glucuronide and sulphate (Parkinson, 1996a). Conjugation of hydroxyl and carboxyl groups with glucuronide and sulphate and subsequent urinary excretion is expected to compete with the other metabolic reactions described in this annex. Based on the metabolic profiles available, these conjugation reactions apparently comprise a small fraction of the overall metabolic disposition of short- and medium-length branched chain alcohols, acids, aldehydes and esters. Conjugation with glucuronide may account for the elimination of up to 10% of the dose, for linear aliphatic alcohols with a chain length of about 6 to 8 carbon atoms. For linear alcohols with shorter chain length, this conjugation with glucuronic acid is even less important (Kamil et al., 1953a).

II.2.5. beta-Oxidation of linear carboxylic acids

beta-Oxidation is a major route of metabolism for the candidate chemicals included in this monograph. beta-Oxidation of fatty acids produces acetyl coenzyme A as a result of sequential removal of two-carbon units from carboxylic acids. The process is repeated until the end products are acetate or propionate. The products of fatty acid oxidation depend on the chain length of the chemical. Acetyl coenzyme A is utilised for energy via the citric acid cycle or converted to acetoacetate and subsequently to other ketone bodies. Ketone bodies may be oxidised or excreted in the urine. Propionate originates from odd numbered-chain acids and is converted to succinyl-CoA for entry into the citric acid cycle (Voet & Voet, 1990). The candidate chemicals included in this monograph are prime candidates for fatty acid beta-oxidation since the esters are expected to be hydrolysed to acids and alcohols, and the alcohols and aldehydes will be oxidised to carboxylic acids.

II.2.6. omega-Oxidation of carboxylic acids

Medium- and long-chain fatty acids also may be partly oxidised via omega-oxidation, producing dicarboxylic acids, which may be attacked from either end by beta-oxidation. omega-Oxidation may occur when capacity for beta-oxidation is either exceeded because of a large dose of the chemical or blocked because of substitution in the alpha or beta position. Short-chain acids, such as butyric, caproic and caprylic acids may be converted to longer-chain fatty acids for incorporation into normal intermediary metabolism (Voet & Voet, 1990).

II.2.7. Other biotransformation reactions

2-Methylbutan-1-ol [FL-no: 02.076]

This and other short chain amyl alcohols were rapidly metabolised after peritoneal injection to rats (1g/kg). The alcohols were oxidised to their corresponding aldehydes, which were assumed to be further oxidised to their corresponding acids (Haggard et al., 1945). The oxidation of alcohols to aldehydes appeared to occur mainly in the liver, for this reaction was inhibited in partially hepatectomized rats. As a minor pathway, primary alcohols may be conjugated directly with glucuronide. In a study of the glucuronic acid conjugation of aliphatic alcohols in rabbit, 2-methylbutanol yielded about 10% of non-reduced glucuronide. Non-branched primary alcohols (C1-C18) showed a very low extent of conjugation (less than 10%) while some branched primary alcohols were conjugated to much higher percentages (Kamil et al., 1953a).

II.3. Conclusion

It is anticipated that the 35 candidate esters [FL-no: 09.307, 09.327, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.587 - 09.589, 09.592 - 09.594, 09.598, 09.600, 09.602, 09.642, 09.651, 09.659 - 09.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, and 09.820] will undergo hydrolysis to yield their corresponding linear or branched chain aliphatic alcohols and linear carboxylic acids. The hydrolysis products of the 35 esters, the four linear aliphatic alcohols [FL-no: 02.126, 02.154, 02.196, and 02.202], the one branched-chain alcohol [FL-no: 02.180] and the one candidate linear aldehyde [FL-no: 05.152], are all expected to be absorbed rapidly from the gastrointestinal tract. Any remaining non-hydrolysed candidate esters are expected to be absorbed rapidly from the gastrointestinal tract as well, after which they are also expected to be hydrolysed.

Linear alcohols, resulting from ester hydrolysis and the four primary linear candidate alcohols, would be oxidised to their corresponding aldehydes and these and the one candidate linear aldehyde would be oxidised to their linear carboxylic acids, which can be assumed to be metabolised to carbon dioxide via the fatty acid pathways and the tricarboxylic acid cycle.

Branched-chain alcohols, resulting from ester hydrolysis and the one primary branched-chain candidate alcohol, would be oxidised to their corresponding aldehydes and further to their corresponding branched chain carboxylic acids, which can be assumed to be metabolised to carbon dioxide via the fatty acid pathways and the tricarboxylic acid cycle. Metabolism to glucuronides may also take place.

Similarly, linear carboxylic acids resulting from ester hydrolysis can be assumed to be metabolised to carbon dioxide via the fatty acid pathways and the carboxylic acid cycle.

Annex III: Toxicity

Acute toxicity data are available for some of the candidate substances of the present flavouring group of 41 substances from chemical groups 1 and 2, and related substances evaluated at the 46th and 49th JECFA meetings (JECFA, 1997a; JECFA, 1998). The supporting substances are listed in brackets.

Table III.1: Acute Toxicity Studies

Chemical Name [FL-no]	Species	Sex	LD50 (mg/kg bw)	Reference	Comments
Methyl formate [09.642]	Rat	NR	1500	(BASF AG, 1979)	
	Rat	NR	475	(Eastman Kodak Co., 1994a)	
	Mouse	NR	475	(Eastman Kodak Co., 1994a)	
	Rabbit	NR	1600	(Munch, 1972)	
	Rabbit	NR	1600	(Gosselin et al., 1984)	
	Rabbit	NR	1622	(RTECS, 2002)	
(Formic Acid [08.001])	Rat	NR	1830	(Sporn et al., 1962)	2
	Mouse	NR	1100	(Malorny, 1969a)	2
(Isoamyl formate [09.162])	Rabbit	NR	3020	(Munch, 1972)	2
	Rat	NR	9840	(Jenner et al., 1964)	2
(Methyl acetate [09.023])	Rat	NR	>5000	(Moreno, 1976c)	1
	Rat	NR	6970	(Smyth et al., 1962)	1
	Rabbit	NR	3700	(Munch, 1972)	1
(Lauryl acetate [09.010])	Rat	NR	>5000	(Moreno, 1974)	1
(cis-3-Hexenyl acetate [09.197])	Rat	NR	>5000	(Wohl, 1974)	1
	Rat	NR	5000	(Sauer & Robbins, 1979)	1
	Rabbit	NR	4750	(Munch, 1972)	1
(10-Undecen-1-yl acetate [09.214])	Rat	NR	>5000	(Levenstein, 1974)	1
(Isobutyl acetate [09.005])	Rat	NR	>13,400	(Smyth et al., 1962)	1
(2-Ethylhexyl acetate [09.381])	Rat	NR	3000	(Smyth & Carpenter, 1944)	1
(Methyl propionate [09.134])	Rat	NR	5000	(Moreno, 1977b)	1
	Mouse	NR	3460	(Lewis, 1996)	1
	Rabbit	NR	2025	(Munch, 1972)	1
(Amyl butyrate [09.044])	Rat	NR	12,200	(Jenner et al., 1964)	1
	Guinea pig	NR	11,900	(Jenner et al., 1964)	1
(Hexyl butyrate [09.045])	Rat	NR	>5000	(Moreno, 1977b)	1
(Heptyl butyrate [09.166])	Rat	NR	>5000	(Moreno, 1982)	1
(Decyl butyrate [09.047])	Rat	NR	9,800	(Smyth et al., 1951)	1

Table III.1: Acute Toxicity Studies, continued

Chemical Name [FL-no]	Species	Sex	LD50 (mg/kg bw)	Reference	Comments
(cis-3-Hexenyl butyrate [09.270])	Rat	NR	>5,000	(Moreno, 1978b)	1
(Isobutyl butyrate [09.043])	Rabbit	NR	9,520	(Munch, 1972)	1
	Rat	NR	>5,000	(Moreno, 1975b)	1
4-Methylpentan-1-ol [02.180]	Rat	NR	6,500	(Wang & Bai, 1998)	
(Methyl valerate [09.182])	Rat	NR	>5,000	(Moreno, 1978b)	1
(cis-3-Hexenyl hexanoate [09.197])	Rat	NR	>5,000	(Moreno, 1978b)	1
(Isobutyl hexanoate [09.064])	Rat	NR	>5,000	(Moreno, 1975b)	1
(Methyl heptanoate [09.096])	Rat	NR	>5000	(Moreno et al., 1981)	1
(Isobutyl heptanoate [09.092])	Rat	NR	>5000	(Moreno, 1976c)	1
	Rat	NR	>2000	(Potokar, 1988)	1
(Methyl decanoate [09.251])	Rat	NR	>2000	(Kästner, 2000b)	Assumes a density of 1 g/ml.
Tetradecan-1-ol [02.126]	Rat	NR	>5000	(Opdyke, 1975, 1977-1979 & 1988)	
	Rat	NR	33000	(Wang & Bai, 1998)	
	Rat	NR	8000	(Egan & Portwood, 1974)	
Heptadecan-1-ol [02.154]	Rat	NR	51600	(Wang et al., 1998)	
Octadecan-1-ol [02.196]	Rat	NR	>5000	(Kästner, 2000a)	
	Rat	NR	>8000	(Egan & Portwood, 1974)	
(Butyl stearate [09.246])	Rat	M	>32000	(Smith, 1953)	1

NR = not reported; M = Male.

1. Summarised by JECFA, 49th meeting (JECFA, 1998)

2. Summarised by JECFA 46th meeting (JECFA, 1997a)

Subacute/subchronic/chronic/carcinogenicity data are available for one candidate substance and for several supporting substances of the present flavouring group. The supporting substances were all evaluated at the 46th, 49th and 51st JECFA meetings (JECFA, 1997a; JECFA, 1998; JECFA, 1999a). The supporting substances are listed in brackets.

Table III.2: Subacute / Subchronic / Chronic / Carcinogenicity Studies

Chemical Name [FL-no]	Species/Sex	Route	Duration (days)	NOEL (mg/kg/day)	Reference	Comments
(Formic Acid [08.001])	Rat/ NR	Diet	42	<1250	(Sporn et al., 1962)	2
	Rat/ NR	Drinking water	42	250	(Sporn et al., 1962)	2
	Rat/ NR	Drinking water	7-189	160	(Sollmann, 1921)	2
	Human/ M	Oral	28	>8	(Sollmann, 1921)	2
(Ethyl formate [09.072])	Rat/ M, F	Diet	119	1000	(Hagan et al., 1967)	2
(Butyl acetate [09.004])	Rat/ NR	Oral	180	>0.5	(Petrovskaya & Bul'bin, 1969)	1
(Octyl acetate [09.075])	Rat/ M, F	Gavage	90	500	(Daughtrey et al., 1989a)	1
(2-Methyl-1-propanol [02.001])	Rat/ M, F	Drinking water	90	>1450	(BASF, 1992)	1
(Methyl butyrate [09.038])	Rat/ M, F	Diet	84	>300	(Alfin-Slater et al., 1965)	1
(Amyl butyrate [09.044])	Rat/ M, F	Diet	112	1000	(Hagan et al., 1967)	1
(3-Methylbutyl alcohol [02.003])	Rat/ M, F	Gavage	119	>1000	(Carpanini et al., 1973)	2
(Ethyl pentanoate [09.147])	Rat/ M, F	Diet	119	1000	(Hagan et al., 1967)	2
(Hexyl alcohol [02.005])	Rat/ M, F	Diet	90	577	(Eibert, 1992)	1
	Dog/ M, F	Gelatin capsules	90	230	(Eibert, 1992)	1
(Methyl hexanoate [09.069])	Rat/ M, F	Diet	84	>300	(Alfin-Slater et al., 1965)	
(cis-3-Hexenol [02.056])	Rat/ M, F	Drinking water	98	150	(Gaunt et al., 1969)	3
(Ethyl heptanoate [09.093])	Rat/ M, F	Diet	90	1000	(Hagan et al., 1967)	2
(Methyl octanoate [09.117])	Rat/ M, F	Diet	84	>300	(Alfin-Slater et al., 1965)	1
	Rat/ M, F	Diet	90	>3.6	(Oser et al., 1965)	1
(Ethyl octanoate [09.111])	Rat/ M, F	Diet	119	1000	(Hagan et al., 1967)	2
(Ethyl nonanoate [09.107])	Rat/ M, F	Diet	112	1000	(Hagan et al., 1967)	2
	Rat/ M, F	Diet	112	>1000	(FDA, 1954)	2
(Methyl decanoate [09.251])	Rat/ M, F	Diet	84	>300	(Alfin-Slater et al., 1965)	
(Methyl laurate [09.101])	Rat/ M, F	Diet	84	>300	(Alfin-Slater et al., 1965)	1
(Dodecan-1-ol [02.008])	Rat/ M, F	Diet	37	100	(Institute of Toxicology, 1992a)	1
(Methyl myristate [09.106])	Rat/ M, F	Diet	84	>300	(Alfin-Slater et al., 1965)	1
Octadecan-1-ol [02.196]	Rat/ M, F	Gavage	28	>1000	(Potokar, 1986)	
(Ethyl acetate [09.001])	Rat/ M, F	Drinking water	371-392	>4	(Johannsen & Purchase, 1969)	2
(Butyl stearate [09.246])	Rat/ M	Diet	730	>3100	(Smith, 1953)	1, No dose-related effect, including no histological changes, even at highest dose: 6.25% corresponding to 3100 mg/kg bw/day.

NR = Not reported; M = male; F = Female.

1. Summarised by JECFA, 49th meeting (JECFA, 1998)

2. Summarised by JECFA 46th meeting (JECFA, 1997a)

3. Summarised by JECFA 51st meeting (JECFA, 1999a)

Developmental and reproductive toxicity data for one candidate substance of the present flavouring group of 41 candidate substances, and for four supporting substances for the present flavouring group evaluated at the 49th JECFA meeting (JECFA, 1998; JECFA, 1999b). The supporting substances are listed in brackets.

Table III.3: Developmental / Reproductive Toxicity Studies

Chemical name	**Study type/ Duration**	**Species/ sex**	**Route**	**NOEL mg/kg/day**	**Effects**	**Reference**	**Comments**
(Butyl acetate [09.004])	Multigeneration repro./ 8 months	Rat/M,F	Gavage	>590	No statistically significant changes in the number of pregnancies, the number of born offspring, the number of viable offspring, the birth weight of offspring or the weight of offspring after 7 and 21 days.	(Sporn et al., 1963)	1
(Octyl acetate [09.007])	Dev. Toxicity/ Day 6 to 15 of gestation	Rat/F	Gavage	Maternal NOEL 100 Develop. NOEL 500	Decreased maternal body weight and food consumption at >500 mg/kg/day. Increased incidence of litters with at least one malformed fetus at 1000 mg/kg/day.	(Daughtrey et al., 1989b)	1
(Dodecan-1-ol [02.008])	One generation repro./ 14 days premating. 5 weeks total	Rat/M,F	Diet	>2000	No effects on reproductive or developmental parameters.	(Institute of Toxicology, 1992a)	1
Octadecan-1-ol [02.196]	One generation repro./ 14 days premating; 5 weeks total	Rat/M,F	Diet	>2000	No effects on reproductive or developmental parameters.	(Institute of Toxicology, 1992b)	
(Butyl stearate [09.246])	One generation repro./ 10 weeks premating	Rat/M,F	Diet	>3100	No adverse effects on fertility, litter size or survival of offspring observed.	(Smith, 1953)	1

F = Female; M = Male.

1. Summarised by JECFA, 49th meeting (JECFA, 1998)

In vitro mutagenicity/genotoxicity data available for candidate substances of the present flavouring group of 41 substances, and supporting substances evaluated at the 46th and 49th JECFA meeting (JECFA, 1997a; JECFA, 1998). The supporting substances are listed in brackets.

Table III.4: Genotoxicity Studies (*In Vitro*)

Chemical Name [FL.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
Methyl formate [09.642]	Ames	S. typh. TA1535, TA100, TA1537, TA98	20-5000µg/plate	Neg.	(BASF AG, 1990)	With and without metabolic activation.
	Ames	S. typh. TA100, TA1535, TA97, TA98	100-10,000µg/plate	Neg.	(Zeiger et al., 1992)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	667-10,000µg/plate	Neg.	(Hoechst-Celanese Corp., 1989a)	With and without metabolic activation.
(Isoamyl formate [09.162])	Rec assay	B. subtilis	Up to 18µg/disk	Neg.	(Oda et al., 1978)	2
	Rec assay	B. subtilis	20 µl/disk in DMSO	Neg.	(Yoo, 1986)	2, With and without metabolic activation.
	Chrom. Abs	CHO fibroblast	Up to 2 mg/ml in DMSO	Neg.	(Ishidate et al., 1984)	2, Without metabolic activation.
	Ames	S.typh. TA92, TA1535, TA100, TA1537, TA94, TA98, TA2637	Up to 10 mg/plate in	Neg.	(Ishidate et al., 1984)	2, With and without metabolic activation.
(Methyl acetate [09.023])	Ames	S. typh. TA97, TA98, TA102, TA104, TA1535, TA1538	Up to 10 mg/plate	Neg.	(Zeiger et al., 1992)	1, With and without metabolic activation.
	Ames	S. typh. TA98, TA100,TA1535, TA1537,TA1538	NR	Neg.	(Hoechst AG., 1988)	1, With and without metabolic activation.
	Ames	E. coli	NR	Neg.	(Hoechst AG., 1988)	1, With and without metabolic activation.
	Induction of aneuploidy	S. cerevisiae D61.M	Up to 3.85 %	See comments	(Zimmermann et al., 1985)	1, Only pos. after cold-shock during mitosis
	Mitotic recomb. and point mutation	S. cerevisiae D61.M	Up to 3.85 %	Neg.	(Zimmermann et al., 1985)	1
(Propyl acetate [09.002])	Induction of aneuploidy	S.cerevisiae D61.M	Up to 1.23%	See comments	(Zimmermann et al., 1985)	1, Only pos. at cytotoxic levels
(Butyl acetate [09.004])	Chrom. Abs.	CH fibroblast cells	2 mg/ml in DMSO	Neg.	(Ishidate et al., 1984)	1, Without metabolic activation.
	Ames	S. typh. TA97, TA98, TA102, TA104, TA1535,TA1538	Up to 10 mg/plate in DMSO	Neg.	(Zeiger et al., 1992)	1, With and without metabolic activation.
	Ames	S.typh. TA92, TA94, TA98, TA100, TA1535, TA1537, TA2637	Up to 10 mg/plate in DMSO	Neg.	(Ishidate et al., 1984)	1, With and without metabolic activation.
	Mod. Ames	S.typh. TA98, TA100, TA1535, TA1537, TA1538, E.coli WP2, uvrA	1-5000 µg/plate	Neg	(Shimizu et al., 1985)	1, With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	NR	Neg.	(Huels, 1988)	1, With and without metabolic activation.
	Induction of aneuploidy	S.cerevisiae D61.M	2.5 to 4.0 mg/ml	Neg.	(Zimmermann et al., 1985)	1, Without metabolic activation.
(Isobutyl acetate [09.005])	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	Up to 5000 µg/ml	Neg.	(Huels-Bericht, 1988)	1, With and without metabolic activation.

Table III.4: Genotoxicity Studies (*In Vitro*), continued

Chemical Name [FL.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
(Methyl octanoate [09.117])	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	1.5 – 5000 µg/plate	Neg.	(Banduhn, 1988)	1, With and without metabolic activation.
(Methyl decanoate [09.251])	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	1.5-5000 µg/plate	Neg.	(Banduhn, 1988)	With and without metabolic activation.
(Methyl laurate [09.101])	Ames	S. typh. TA98, TA100, TA1535, TA1538, C12	NR	Neg.	(Banduhn, 1992a)	1, With and without metabolic activation.
Tetradecan-1-ol [02.126]	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	1.5 – 5000 µg/plate	Neg.	(Wallat, 2000b; Wallat, 2000a)	With and without metabolic activation.
Octadecan-1-o l[02.196]	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	0.63 – 20 µg/plate	Neg.	(Wallat, 2000c)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	50 µg/plate	Neg.	(Anonymous, 1985a)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	0.033-10 mg/plate	Neg.	(Prival et al., 1991)	With and without metabolic activation.
	Ames	E. coli, WP2	0.033-10 mg/plate	Neg.	(Prival et al., 1991)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	0.3-10,000 µg/plate (TA100); 10 – 3333 µg/plate (other strains)	Neg.	(Mortelmans & Tanaka, 1989)	With and without metabolic activation.
	Ames	E. coli, WP 2	10-3333 mg/plate	Neg.	(Mortelmans & Tanaka, 1989)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537	0.3 µmol/plate	Neg.	(Florin et al., 1980)	With and without metabolic activation.
(Butyl stearate [09.246])	Reversion Assay	S. typh. TA97, TA98, TA100, TA102, TA1537, E. coli, WP2	100-5000µg/plate in acetone with Tween 80	Neg.	(Hachiya, 1987)	1, With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	0.04-4 µl/plate	Neg.	(Mobil Oil Corp., 1982)	1, With and without metabolic activation.

NR = Not reported.

1. Summarised by JECFA, 49th meeting (JECFA, 1998)

2. Summarised by JECFA, 46th meeting (JECFA, 1997a)

In vivo mutagenicity/genotoxicity data are only available for three supporting substances evaluated at the 49th JECFA meeting (JECFA, 1998).

Table III.5: Genotoxicity Studies (*In Vivo*)

Chemical Name	Test System	Test Type	Route	Dose	Result	Reference	Comments
(Methyl acetate [09.023])	Humans	SCE & Chrom. Aberrations (Occ. exp.)	Inhalation	3-169 mg/m^3	Negative	(Haglund et al., 1980)	1
(Butyl acetate [09.004])	Humans	SCE & Chrom. Aberrations (Occ. exp.)	Inhalation	7-1676 mg/m^3	Negative	(Haglund et al., 1980)	1
(Dodecan-1-ol [02.008])	Mouse	Micronucleus	gavage	5000 mg/kg bw	Negative	(Banduhn, 1992b)	1

1. Summarised by JECFA, 49th meeting (JECFA, 1998)

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